Yeast Model for Cystinosis

Progress Report
March 2011

Seasson P. Vitiello and David A. Pearce

The single-celled eukaryote *Saccharomyces cerevisiae* (budding yeast) is a useful model system because many pathways and protein functions are conserved from yeast to humans and it is amenable to genetic manipulations and biochemical analyses. The functional ortholog of cystinosin is Ers1p, which is encoded by the *ERS1* gene. We have been working several projects to identify and explore the cellular defects that occur when *ERS1* is absent in the *ers1*-Δ yeast strain. Our overall objective is to identify pathways and proteins that compensate for the absence of Ers1p in the *ERS1* deletion strain *ers1-Δ* and explore how these pathways may be interacting with *ERS1* and exhibiting their buffering effect.

In our most recent report where you graciously agreed to continue support for Kristen Robinson we highlighted our curious findings on release of hydrogen sulphide from yeast strains bearing deletion of ERS1, in combination with other gene deletions. We are still characterizing this interesting find and are focusing on delineating the role of methionine metabolism with this phenomenon. Methionine as you know is another sulphur containing amino acid.

In this report I list the preliminary analysis of our microarray studies where we compared gene expression of all yeast transcripts in wild type and *ers1-Δ*.

In summary, we compared mid-log phase grown on minimal media. Triplicate samples were independently grown and analyzed. Cells are actively growing at this point so the fundamental consequences of lacking Ers1p are revealed. Based on our previous studies we are convinced that Ers1p is a cystine efflux protein, but that yeast have the ability to compensate in some way to avoid accumulation of cystine in the vacuole/lysosome. The observation that certain strains lacking Ers1p produce hydrogen sulphide support this. The microarray studies were designed to assist in identifying the mechanism for compensation. table 1 shows the statistically significant changes from this experiment. We will be repeating this experiment at other growth stages and through comparison of just wild type strains at different growth stages hope to refine the list of genes that we will follow up with.

Cursory analysis shows that genes associated to glutathione metabolism as well as other transport proteins have altered expression. The next few moths will fiocus of deducing which of these gene expression changes contributes to the compensatory mechanism of avoiding cystine accumulation

Table 1. Gene expression changes when comparing wild type and ers1-Δ.

fold change	Transcript ID	Gene Symbol
-4.18433976	YOL162W	---
-5.70410287	YAL067C	SEO1
-2.27205853	YLR364W	GRX8
2.256364275	YHR139C	SPS100
-2.39495741	YGR087C	PDC6
-2.65001403	YBL101W-A	---
-2.35381347	YBR040W	FIG1
-3.56524198	YHR126C	ANS1
-2.06193664	YPL192C	PRM3
-2.22221746	YHR176W	FMO1
2.300583787	YFR015C	GSY1
-5.33319471	YFL055W	AGP3
-85.3902829	**YCR075C**	**ERS1**
-2.27363395	YCL073C	---
-2.64634288	YLL055W	YCT1
-4.73708645	YOL163W	---
-2.13465068	YLL062C	MHT1
-4.26930135	YOL164W	BDS1
-2.25636427	YML047C	PRM6
2.659214216	YER067W	---
2.137611982	YGL263W	COS12
-12.3291377	YLL057C	JLP1